university of groningen

University Medical Center Groningen

University of Groningen

Surface Area of Detachment, Proliferative Vitreoretinopathy, and Pulse Pressure, but not AGEs, are Associated With Retinal Redetachment

Fokkens, Bernardina T.; Mulder, Douwe J.; Nugteren, Michiel B.; Schalkwijk, Casper G.; Scheijen, Jean L.; Smit, Andries J.; Los, Leonoor I.

Published in:
Investigative ophthalmology & visual science

DOI:
10.1167/iovs.16-20735

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Fokkens, B. T., Mulder, D. J., Nugteren, M. B., Schalkwijk, C. G., Scheijen, J. L., Smit, A. J., & Los, L. I. (2016). Surface Area of Detachment, Proliferative Vitreoretinopathy, and Pulse Pressure, but not AGEs, are Associated With Retinal Redetachment. *Investigative ophthalmology & visual science*, *57*(15), 6633-6638. https://doi.org/10.1167/iovs.16-20735

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Surface Area of Detachment, Proliferative Vitreoretinopathy, and Pulse Pressure, but not AGEs, are Associated With Retinal Redetachment

Bernardina T. Fokkens,[1–3] Douwe J. Mulder,[1] Michiel B. Nugteren,[3] Casper G. Schalkwijk,[4] Jean L. Scheijen,[4] Andries J. Smit,[1,2] and Leonoor I. Los[3,5]

[1]Department of Internal Medicine, University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands
[2]Research Institute GUIDE, Graduate School of Medical Sciences, University of Groningen, Groningen, The Netherlands
[3]Department of Ophthalmology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands
[4]Laboratory for Metabolism and Vascular Medicine, Experimental Internal Medicine, Maastricht University, Maastricht, The Netherlands
[5]W.J. Kolff Institute, Graduate School of Medical Sciences, University of Groningen, Groningen, The Netherlands

Correspondence: Bernardina T. Fokkens, University Medical Center Groningen, Department of Ophthalmology, HPC BB60, P.O. Box 30 001, 9700 RB Groningen, The Netherlands;
bt.fokkens@umcg.nl.

Submitted: September 12, 2016
Accepted: November 1, 2016

Citation: Fokkens BT, Mulder DJ, Nugteren MB, et al. Surface area of detachment, proliferative vitreoretinopathy, and pulse pressure, but not AGEs, are associated with retinal redetachment. *Invest Ophthalmol Vis Sci*. 2016;57:6633–6638. DOI: 10.1167/iovs.16-20735

Purpose. Advanced glycation endproducts (AGEs) have been suggested to play a role in retinal redetachment by promoting proliferative vitreoretinopathy (PVR). The purpose of this study was to investigate whether AGEs, in combination with other clinical characteristics, were able to identify patients at high risk for redetachment after vitrectomy for rhegmatogenous retinal detachment (RRD).

Methods. In this prospective cohort study, 410 RRD patients were included. Skin autofluorescence (SAF), as a reflection of tissue AGE accumulation, was measured by the AGE Reader. In a subgroup of 90 patients, the well characterised AGEs N^{ε}-(carboxymethyl)lysine (CML), N^{ε}-(carboxyethyl)lysine (CEL), 5-hydro-5-methylimidazolone (MG-H1), and pentosidine, and the α-dicarbonyls methylglyoxal, glyoxal, and 3-deoxyglucosone were measured in vitreous biopsies using ultra- or high-performance liquid chromatography. The main outcome was retinal redetachment within 3 months after surgery.

Results. Fifty-three patients developed a redetachment (aged 64 ± 9.6, 64% male) and were compared with 352 patients without a redetachment (aged 61 ± 9.4, 69% male); five patients were excluded for various reasons. Univariable analysis revealed that SAF, vitreous AGEs, and vitreous α-dicarbonyls were not significantly elevated in patients with a redetachment. Multivariable logistic regression analysis showed that surface area of detachment greater than 50% (odds ratio [OR] 2.74, confidence interval [CI] 1.45–5.17), PVR grade C (OR 4.57, CI 1.68–12.42), and pulse pressure (OR 1.37, CI 1.03–1.83 per SD) were independently associated with the occurrence of redetachment.

Conclusions. Skin autofluorescence and vitreous AGEs are not suitable to identify patients at high risk for redetachment after vitrectomy surgery. Surface area of detachment greater than 50%, PVR grade C, and pulse pressure were associated with redetachment.

Keywords: skin autofluorescence, advanced glycation endproducts, rhegmatogenous retinal detachment, proliferative vitreoretinopathy, pulse pressure

Rhegmatogenous retinal detachment (RRD) is a sight-threatening disease with an annual incidence of 18.2 per 100,000 in The Netherlands.[1] Surgical treatment results in primary reattachment of the retina in 64% to 94% of cases.[2] Persistent detachments and redetachments are associated with poor functional results. To some extent, preoperative findings can be used to individualize the chance of success. An important risk factor for redetachment is proliferative vitreoretinopathy (PVR).

Attempts to improve the outcome of surgical treatment of RRD have been made by the intravitreal use of drugs in order to prevent PVR. However, due to mixed results and/or retinal toxicity, none of these have led to a safe or sufficiently effective drug for routine use. Therefore, several studies have emphasized the need to identify high-risk patients who may benefit from a specific treatment. Because of the complexity of risk factors associated with the development of PVR, it is difficult to identify patients at high risk.[3]

One factor that may play a role in retinal redetachment is increased tissue glycation and the accumulation of advanced glycation endproducts (AGEs), which are formed by glycation and oxidation of free amino groups of proteins, lipids, and nucleic acids. AGEs and their α-dicarbonyl precursors play a role in several age-related conditions, such as atherosclerosis and diabetes mellitus.[4] Moreover, AGEs have been found at sites of known ocular pathology.[5] Currently, little is known about AGEs in RRD patients, but some evidence exists for a role of AGEs in the development of PVR.[6] Both AGEs and AGE-

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

Downloaded From: http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/935913/ on 03/02/2017

Investigative Ophthalmology & Visual Science

receptors (RAGE) were increased in the vitreous of patients with PVR and were present in their epiretinal membranes (ERMs).[7] Furthermore, AGEs can induce the expression of several cytokines that have been shown to be elevated in PVR.[8–10]

Considering the potential role of AGEs in PVR, AGEs might represent a risk factor for retinal redetachment. AGE accumulation can be estimated by skin autofluorescence (SAF), a noninvasive technique that reflects AGE accumulation in several tissues with slow turnover, such as the skin[11,12] and cardiac tissue.[13] Skin autofluorescence is related to autofluorescence of the lens and is elevated in patients with neovascular AMD and diabetic retinopathy.[5]

The primary objective of the present study was to investigate whether SAF, in combination with other clinical characteristics, was able to identify patients at high risk for retinal redetachment after vitrectomy. The secondary objective was to investigate several vitreous AGEs and α-dicarbonyls in a subgroup of patients in order to evaluate the potential relation of systemic AGE accumulation with local eye disease.

Methods

This study was designed as a prospective cohort study consisting of RRD patients who were scheduled for trans pars plana vitrectomy (TPPV) surgery. The research protocol was approved by the Medical Ethics Committee of the University Medical Center Groningen (UMCG; The Netherlands) and adhered to the Declaration of Helsinki. The study was registered in the Dutch Trial Register (NTR4289) and was performed at the UMCG between November 2013 and August 2015. All participants gave their written informed consent.

Study Population

Adult patients visiting the Ophthalmology Department of the UMCG and presenting with an RRD were invited to participate in this study. Patients who were scheduled for primary TPPV, but also patients undergoing vitrectomy after earlier cryotherapy, photocoagulation, or scleral buckling procedures for retinal breaks or small detachments, were included. The following exclusion criteria were based on the presence of conditions that are known to affect AGE levels or SAF measurements: known renal disease with impairment of renal function, dialysis treatment, history of renal transplantation,[14] current infection or active inflammatory disease,[15] skin abnormalities on both forearms, and dark colored skin with reflectance less than 8%. Clinical data and general characteristics were obtained by chart review and questionnaires. The smoking variable was divided into two groups: (1) never smoker and previous smoker, and (2) current smoker. General practitioner data were obtained for medical history of the patients and pharmacy data were obtained for medication use. Using a sphygmomanometer, blood pressure was measured in a seated position by auscultation of the brachial artery. Pulse pressure, as a global systemic measure for arterial stiffness, was calculated as systolic blood pressure minus diastolic blood pressure.

Standard Laboratory Assessments

Nonfasting venous blood was collected by venipuncture. Serum creatinine, C-reactive protein (CRP), plasma glucose, and HbA1c were measured using standard procedures. Renal function was evaluated by estimated glomerular filtration rate (eGFR) calculated by the modification of diet in renal disease formula: $eGFR = 186 \times [\text{serum creatinine } (\mu M) \times 0.0113]^{-1.154} \times \text{age}^{-0.203}$ ($\times$ 0.742 for women). C-reactive protein was measured to ensure that no active infection or inflammatory disease was present, because this could affect AGE accumulation.[15] Diabetes mellitus was defined by criteria from the American Diabetes Association[16] or twice measured values of HbA1c greater than or equal to 48 mmol/mol.

Vitrectomy Procedure

At the start of a standard three-port trans pars plana vitrectomy procedure, undiluted vitreous samples were collected from the midvitreous by aspirating the vitreous manually through a syringe connected to the vitrectome. The samples were frozen within 15 to 30 minutes and stored at –80°C until further use. After fluid-air exchange and subretinal fluid drainage from the causative retinal tear(s) or iatrogenic hole, intraoperative laser coagulation, and/or cryotherapy were applied to the causative retinal tear(s) and/or iatrogenic hole. Based on clinical presentation, either 20% sulfur hexafluoride (SF6), 15% octafluorpropane (C3F8), or 5000 centistokes silicone oil was used as tamponade agent. In case of silicone oil, a second procedure was needed to remove the oil. Individual features of the surgery, such as use of cryotherapy or internal limiting membrane peeling, were documented in the surgical report.

Ophthalmic Characteristics

Characteristics of retinal detachment were determined during surgery. Surface area of detached retina in relation to total retinal surface was scored in quartiles. Proliferative vitreoretinopathy (PVR) was graded A to C, according to the Retina Society PVR classification.[17] The number of retinal defects and presence of vitreous bleeding were also scored. Furthermore, duration of detachment was approximated by asking the patient about duration of visual field loss. Our main outcome was defined as a redetachment within 3 months after the vitrectomy procedure. In case of silicone oil use, the main outcome was defined as a redetachment within 3 months after removal of the oil. The timeframe of 3 months was chosen because redetachments due to PVR usually occur shortly after the tamponade no longer exerts pressure to the retina. Furthermore, the majority of redetachments of all causes (85%) occur within 90 days after vitrectomy.[18]

Skin Autofluorescence

Skin autofluorescence was measured on the left forearm using the AGE Reader (DiagnOptics Technologies BV, Groningen, The Netherlands), a noninvasive desktop device using the characteristic fluorescent properties of certain AGEs to estimate the level of AGE accumulation in the skin. Technical details concerning the optical technique have been extensively described elsewhere.[19] Because SAF measurements may be influenced by the use of skin products,[20] patients were asked about their recent use. When patients used skin tanners up to 14 days or sunscreen up to 7 days before SAF measurements, SAF measurements were repeated on another day. When patients used body lotion or other skin products up to 4 days before SAF measurements, the lower arm was cleaned with water and soap or alcohol 70%. Skin autofluorescence values are expressed in arbitrary units (AU).

Measurement of AGEs and α-Dicarbonyls in Vitreous Samples

Vitreous samples of 45 patients with a retinal redetachment were analysed and compared with samples of 45 patients without a redetachment, matched on age,[21] eGFR, diabetes

Investigative Ophthalmology & Visual Science

Downloaded From: http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/935913/ on 03/02/2017

mellitus, smoking,[22] intraocular lens implantation,[6] and PVR.[6,7] Measurement methods of AGEs and α-dicarbonyls have been described in detail elsewhere: pentosidine was measured using HPLC with a fluorescence detector[23]; lysine and protein-bound N^{ε}-(carboxymethyl)lysine (CML), N^{ε}-(carboxyethyl)lysine (CEL), and 5-hydro-5-methylimidazolone (MG-H1) were measured using ultra performance liquid chromatography tandem mass spectrometry (UPLC MS/MS)[24]; derivatized 3-deoxyglucosone (3-DG), methylglyoxal (MGO), and glyoxal (GO) were analyzed by UPLC MS/MS.[25]

Statistical Analysis

A study population with a minimum of 50 subjects with retinal redetachment was pursued to be able to construct a regression model in which correction for five confounders would be allowed. Data are presented in percentages, as mean and SD, or as median and interquartile range (IQR). Differences between redetachment patients and controls were tested using χ^2 tests for categorical variables, *t*-tests for normally distributed continuous variables, and Mann-Whitney *U* tests for remaining variables. Using the backward stepwise method, a multivariable logistic regression model was developed relating risk factors identified by univariable analysis ($P < 0.1$) to the risk of redetachment. Statistical significance was accepted at *P* less than 0.05. Statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA).

Results

A total of 410 RRD patients were included in the study. Before analysis, five patients were excluded: four patients underwent scleral buckling procedures instead of vitrectomy and one patient still had silicon oil in situ at the end of the study. Therefore, 405 patients remained for analysis. Of these patients, 366 underwent vitrectomy, 1 patient underwent a combined vitrectomy/scleral buckling procedure, and 38 underwent a combined vitrectomy/cataract surgery. A redetachment within 3 months occurred in 53 patients, leaving 352 patients in the control group. Clinical and biochemical characteristics of the study population stratified for redetachment and controls are shown in Table 1.

General Characteristics

Patients who developed a redetachment were significantly older, had higher systolic blood pressure, and had higher pulse pressure. Sex, body mass index, smoking, and presence of diabetes mellitus were not different between the two groups.

Ophthalmic Characteristics

More patients with an intraocular lens implantation developed a retinal redetachment compared with phakic patients. Furthermore, retinal detachment surface of greater than 50% was associated with retinal redetachment. Although patients with PVR grades B and C tended toward an association with retinal redetachment, it appeared that only patients with PVR grade C contributed to this association. Detachment duration and number of retinal breaks were not different between the two groups.

Skin Autofluorescence

Before analysis of the relation between skin autofluorescence and redetachment, some additional patients had to be excluded with known confounders for SAF measurement. Two patients were excluded with CRP greater than 20 mg/L and five patients were excluded because of the use of skin products without proper cleaning of the forearm or logistic failure of repeating the measurement on another day. Furthermore, two patients did not have SAF values since SAF could not be measured by the AGE Reader (probably due to reflectance < 8%). Therefore, SAF values of 50 redetachment patients were compared with 346 control patients. Skin autofluorescence did not differ significantly between redetachment patients and controls. After correction for age, eGFR, and diabetes mellitus, SAF values were still comparable between redetachment patients and controls (odds ratio [OR] = 0.79, $P = 0.457$).

Table 1. Clinical and Biochemical Characteristics of the Study Population

Characteristic	Redetachment, $n = 53$*	Control, $n = 352$†	*P* Value
Age, y	64 ± 9.6	61 ± 9.4	0.024
Sex, male, %	64.2	69.3	0.450
BMI, kg/m²	26 ± 4.0	26 ± 3.8	0.925
Systolic blood pressure, mm Hg	135 (130–154)	130 (124–145)	0.017
Pulse pressure, mm Hg	56 (49–65)	50 (45–60)	0.022
Current smoker, %	11.3	13.7	0.639
Diabetes mellitus, %	13.2	9.4	0.383
Intra ocular lens implantation, %	47.2	31.3	0.022
Surface area of detachment >50%, %	62.3	33.4	<0.001
PVR grades B & C, %	22.6	13.1	0.065
PVR grade C, %	17.0	2.8	<0.001
Detachment duration, d	8 (5–17)	7 (5–13)	0.076
Retinal breaks, *n*	2 (1–3)	2 (1–4)	0.252
Vitrectomy/vitrectomy + cataract, %	84.9/15.1	91.5/8.5	0.126
Tamponade gas/oil, %	78.8/21.2	93.8/6.3	<0.001
Cryotherapy, %	81.1	82.4	0.824
ILM peeling, %	34.0	25.3	0.182
Nonfasting glucose, mM	5.9 (5.5–6.5)	5.8 (5.4–6.7)	0.714
HbA1c, mmol/mol	38 (35–42)	38 (36–41)	0.864
eGFR, mL/min	84 ± 17.4	85 ± 15.3	0.562
Skin autofluorescence, AU	2.42 ± 0.46	2.36 ± 0.53	0.431

BMI, body mass index; ILM, internal limiting membrane. For categorical variables, data are displayed as percentages and *P* values are based on χ^2 tests. For normally distributed continuous variables, data are given as mean ± SD and *P* values are based on *t*-tests. For remaining variables, data are shown as median (IQR) and *P* values are based on Mann-Whitney *U* tests.

* For skin autofluorescence, $n = 50$.

† For skin autofluorescence, $n = 346$.

Vitreous AGEs and α-Dicarbonyls

Biochemical characteristics of the vitreous are shown in Table 2. None of the measured protein-bound AGEs, free AGEs, or α-dicarbonyls were significantly elevated in the redetachment patients.

Multivariable Analysis

A binomial logistic regression analysis was performed to ascertain the effects of age, systolic blood pressure, pulse pressure, previous intraocular lens implantation, surface area of detachment, and PVR grade C on the likelihood that participants developed redetachment of the retina. Considering that choice of tamponade strongly depends on clinical

Investigative Ophthalmology & Visual Science

Downloaded From: http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/935913/ on 03/02/2017

Table 2. Match Criteria and Biochemical Characteristics of the Vitreous

Characteristic	Redetachment, $n = 45$	Control, $n = 45$	*P* Value
Age, y	64 ± 9.7	64 ± 9.5	0.948
eGFR, mL/min	84 ± 18.1	86 ± 14.8	0.648
Diabetes mellitus, %	11.1	13.3	0.748
Current smoker, %	13.3	8.9	0.502
Intra ocular lens implantation, %	51.1	46.7	0.673
PVR grades B & C, %	17.8	20.0	0.788
Lysine, mM	0.66 (0.40–1.63)	0.55 (0.39–1.05)	0.451
Protein-bound AGEs			
Pentosidine, nmol/mmol lysine	1.59 (1.24–2.78)	1.91 (1.19–2.70)	0.971
CML, nmol/mmol lysine	227 (176–341)	232 (182–295)	0.696
CEL, nmol/mmol lysine	128 (86–207)	122 (66–164)	0.061
MG-H1, nmol/mmol lysine	670 (452–1434)	698 (352–1076)	0.355
Free AGEs			
CML, nM	77 (56–93)	77 (59–92)	0.580
CEL, nM	66 (53 - 77)	67 (50–82)	0.726
MG-H1, nM	171 (128–224)	179 (125–244)	0.850
α-dicarbonyls			
3-DG, nM	648 (533–787)	602 (523–785)	0.485
MGO, nM	235 (193–270)	234 (200–282)	0.850
GO, nM	426 (248–628)	490 (309–660)	0.300

Data are shown as median (IQR) and *P* values are based on Mann-Whitney *U* tests.

presentation of retinal detachment, tamponade was not kept as a criterium for analysis. Furthermore, the strong correlation between systolic blood pressure and pulse pressure ($r = 0.793$, $P < 0.001$) did not allow both variables in the same model. Therefore, the multivariable analysis was performed twice and the final model was chosen based on Nagelkerke R^2 and model χ^2. In the final model (Table 3), three variables significantly contributed to the prediction of redetachment: pulse pressure, surface area of detachment, and PVR grade C. The model explained 13.3% (Nagelkerke R^2) of the variance in redetachment. Patients with area of detachment greater than 50% had 2.7 higher odds to develop a redetachment than patients with area of detachment less than 50%. Patients with PVR grade C had 4.6 higher odds to develop a redetachment than patients with PVR grades 0 to B.

Discussion

This study addressed whether systemic and vitreous AGE accumulation, in combination with other potential risk factors, including disease characteristics, surgical procedures, and blood pressure, were associated with the development of redetachment after vitrectomy for RRD. The results show that neither SAF nor vitreous AGE levels predicted redetachment in our study population.

Table 3. Parameters of the Multivariable Model Independently Related to Redetachment Less Than 3 Months

Characteristic	OR	95% CI	*P* Value
Surface area of detachment > 50%	2.74	1.45–5.17	0.002
PVR grade C	4.57	1.68–12.42	0.003
Pulse pressure	1.37*	1.03–1.83*	0.031

Nagelkerke $R^2 = 13.3\%$; Model $\chi^2 = 29.21$, $P < 0.001$.
* OR is expressed per 1-SD increase of pulse pressure.

These findings were unexpected, because of the potential role of AGEs in PVR in combination with the anticipated high proportion of redetachments due to PVR. In previous research, a relation has been found between PVR grade and vitreous pentosidine in RRD patients.[6] A pilot study performed by our study group indicated that both SAF and vitreous pentosidine were elevated in patients with PVR grades B or C.[26] Furthermore, both AGEs and RAGE were increased in the vitreous of patients with PVR and were present in their ERMs.[7] The suggested pathway by which AGEs may play a role in PVR is through activation of RAGE in myofibroblasts located in ERMs.[27] These myofibroblasts are proposed to play a key role in fibrosis by contributing to tissue contraction and by producing extracellular matrix components.[28] Furthermore AGEs may play a role in PVR through the induction of several cytokines that are elevated in PVR (e.g., monocyte chemo attractant protein-1 [MCP-1] and VEGF).[8–10]

Several factors should be considered when interpreting our results in the context of previous AGE studies in PVR. In the present study, AGE accumulation was not investigated in patients with redetachments due to PVR alone, but to redetachments of any cause. Furthermore, the selection of tamponade during vitrectomy based on clinical presentation may have played a role. Patients with preoperatively present PVR grades B and C were more likely to receive oil tamponade, which may have reduced the risk of redetachment in these patients. Another important consideration is that 'local' AGEs were measured in the vitreous, which was removed during surgery. Therefore, the measured levels of AGEs may not reflect local AGE levels during the follow-up period. Considering these factors, the results of this study do not exclude a role of AGEs in PVR.

Concerning the risk factors for redetachment that were observed in this cohort study, the results were largely in agreement with previous studies. Although a variety of risk factors have been identified, the extent of detached retina and PVR grade C are characteristics that usually emerge as important risk factors.[29–32] Likewise, our results show that more patients develop a redetachment when the surface area of detachment is greater than 50% and when PVR grade C is present. Concerning increasing age and previous intraocular lens implantation as risk factors for redetachment, mixed results have been shown previously.[29,33] Therefore, it was not surprising that these factors were no longer significant in our multivariable analysis. Probably, these factors contribute to redetachment through influencing other risk factors considering the reciprocal correlations (data not shown). To illustrate, age was correlated with area of detachment ($r = 0.189$, $P < 0.001$) and pulse pressure ($r = 0.308$, $P < 0.001$), and intraocular lens implantation was correlated with area of detachment ($r = 0.165$, $P = 0.001$).

Although arterial stiffness is not often considered as a risk factor for retinal redetachment, our results indicate that pulse pressure independently contributes to the development of redetachment after vitrectomy. If this observation would be confirmed in other cohorts, it could be recommended to screen RRD patients for untreated hypertension and increased pulse pressure in the preoperative evaluation of vitrectomy patients in addition to the establishment of disease characteristics. Though it seems obvious to regulate the blood pressure properly, it should be further investigated whether this would also lead to risk reduction of redetachments. A possible mechanism in which elevated pulse pressure could contribute

Investigative Ophthalmology & Visual Science

Downloaded From: http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/935913/ on 03/02/2017

to redetachments in RRD patients would be comparable to proposed mechanisms in which untreated hypertension could lead to serous retinal detachments[34] and central serous chorioretinopathy[35]: elevated blood pressure leads to increased intravascular pressure, which may cause changes in the retinal pigment epithelium (RPE) that impairs the RPE-mediated drainage of subretinal fluid.

A major strength of the current study is the measurement of several AGEs and α-dicarbonyls with state-of-the-art techniques based on UPLC MS/MS. Moreover, free AGEs were measured in addition to protein-bound AGEs. Because free AGEs are breakdown products of protein-bound AGEs, the absence of elevated levels of free AGEs indicates that the lack of differences in protein-bound CML, CEL, and MG-H1 is not a result of differences in degradation of these products. Furthermore, we prospectively investigated a relatively unselected and large cohort in a single-center study, which would be representative for the Dutch RRD population in the northern part of The Netherlands.

A limitation of our study was the selection of redetachment patients due to any cause instead of PVR only. This choice was made because it would be clinically more relevant to be able to identify any patient with a redetachment than just a subgroup. Also, the follow-up time of 3 months after vitrectomy might be a limitation. However, approximately 85% of the redetachments of all causes occur within 90 days after vitrectomy.[18] For redetachments due to PVR, this proportion is probably even higher. The study size for comparing vitreous levels of AGEs in redetachment patients and matched controls might be too small to detect differences, because our sample size was based on the construction of a regression model for SAF. However, the clinical relevance would be limited if it would be necessary to investigate an even larger cohort. The results concerning free AGEs and α-dicarbonyls could be subject to sampling errors, because the aging vitreous consists of areas of synchisis and syneresis.[36,37] Unfortunately, this is inevitable because there is a limit to the undiluted vitreous that can be removed safely from the eyes of patients, in particular from those with RRD. Finally, since our study was not designed to investigate the influence of pulse pressure on redetachment in RRD patients, this could be a coincidental finding.

In conclusion, SAF and vitreous AGEs are not able to identify patients at high risk of retinal redetachment after vitrectomy surgery. In addition to surface area of detachment greater than 50% and PVR grade C, pulse pressure was observed as a risk factor for redetachment. Before any recommendations can be given, the value of this potential new biomarker should be established in other cohorts of RRD patients.

Acknowledgments

The authors thank Eveline A. Huiskamp, Gina Postma, and Victor W. Renardel de Lavalette for conducting the vitreous sampling.

Supported by grants from 'Stichting Blindenhulp', The Netherlands. This organization had no role in the design or conduct of this research.

Disclosure: **B.T. Fokkens**, None; **D.J. Mulder**, None; **M.B. Nugteren**, None; **C.G. Schalkwijk**, None; **J.L. Scheijen**, None; **A.J. Smit**, DiagnOptics BV (I); **L.I. Los**, None

References

1. Van de Put MA, Hooymans JM, Los LI, et al. The incidence of rhegmatogenous retinal detachment in the Netherlands. *Ophthalmology*. 2013;120:616–622.
2. Ryan SJ. Retinal reattachment: general surgical principles and techniques. In: Ryan SJ, ed. 5th ed. *Retina*. Philadelphia, PA: Elsevier Saunders; 2013:1713.
3. Sundaram V, Barsam A, Virgili G. Intravitreal low molecular weight heparin and 5-Fluorouracil for the prevention of proliferative vitreoretinopathy following retinal reattachment surgery. *Cochrane database Syst Rev*. 2013;1:CD006421.
4. Semba RD, Nicklett EJ, Ferrucci L. Does accumulation of advanced glycation end products contribute to the aging phenotype? *J Gerontol A Biol Sci Med Sci*. 2010;65:963–975.
5. Nagaraj RH, Linetsky M, Stitt AW. The pathogenic role of Maillard reaction in the aging eye. *Amino Acids*. 2012;42:1205–1220.
6. van Deemter M, Bank RA, Vehof J, Hooymans JM, Los LI. Factors associated with pentosidine accumulation in the human vitreous [published online ahead of print July 26 2016]. *Retina*. doi:10.1097/IAE.0000000000001219.
7. Pachydaki SI, Tari SR, Lee SE, et al. Upregulation of RAGE and its ligands in proliferative retinal disease. *Exp Eye Res*. 2006;82:807–815.
8. Leiderman YI, Miller JW. Proliferative vitreoretinopathy: pathobiology and therapeutic targets. *Semin Ophthalmol*. 2009;24:62–69.
9. Inagaki Y, Yamagishi S, Okamoto T, Takeuchi M, Amano S. Pigment epithelium-derived factor prevents advanced glycation end products-induced monocyte chemoattractant protein-1 production in microvascular endothelial cells by suppressing intracellular reactive oxygen species generation. *Diabetologia*. 2003;46:284–287.
10. Lu M, Kuroki M, Amano S, et al. Advanced glycation end products increase retinal vascular endothelial growth factor expression. *J Clin Invest*. 1998;101:1219–1224.
11. Meerwaldt R, Graaff R, Oomen PH, et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia*. 2004;47:1324–1330.
12. Meerwaldt R, Hartog JW, Graaff R, et al. Skin autofluorescence, a measure of cumulative metabolic stress and advanced glycation end products predicts mortality in hemodialysis patients. *J Am Soc Nephrol*. 2005;16:3687–3693.
13. Hofmann B, Jacobs K. Navarrete Santos A, Wienke A, Silber RE Simm A. Relationship between cardiac tissue glycation and skin autofluorescence in patients with coronary artery disease. *Diabetes Metab*. 2015;41:410–415.
14. Stinghen AEM, Massy ZA, Vlassara H, Striker GE, Boullier A. Uremic toxicity of advanced glycation end products in CKD. *J Am Soc Nephrol*. 2016;27:354–370.
15. de Groot L, Hinkema H, Westra J, et al. Advanced glycation endproducts are increased in rheumatoid arthritis patients with controlled disease. *Arthritis Res Ther*. 2011;13:R205.
16. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;26(suppl 1):S5–S20.
17. Thompson J. Proliferative vitreoretinopathy. In: Ryan S, ed. *Retin*. St Louis, MO: Mosby; 2001:2287–2316.
18. Lee E, El Housseini Z, Steel DH, Williamson TH. An analysis of the outcomes for patients with failed primary vitrectomy for rhegmatogenous retinal detachment. *Graefe's Arch Clin Exp Ophthalmol*. 2014;252:1711–1716.
19. Mulder DJ, Water TV, Lutgers HL, et al. Skin autofluorescence, a novel marker for glycemic and oxidative stress-derived advanced glycation endproducts: an overview of current clinical studies, evidence and limitations. *Diabetes Technol Ther*. 2006;8:523–535.
20. Noordzij MJ, Lefrandt JD, Graaff R, Smit AJ. Dermal factors influencing measurement of skin autofluorescence. *Diabetes Technol Ther*. 2011;13:165–170.

Downloaded From: http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/935913/ on 03/02/2017

21. van Deemter M, Ponsioen TL, Bank RA, et al. Pentosidine accumulates in the aging vitreous body: a gender effect. *Exp Eye Res*. 2009;88:1043–1050.
22. van Waateringe RP, Slagter SN, van der Klauw MM, et al. Lifestyle and clinical determinants of skin autofluorescence in a population-based cohort study. *Eur J Clin Invest*. 2016;46:481–490.
23. Scheijen JL, van de Waarenburg MP, Stehouwer CD, Schalkwijk CG. Measurement of pentosidine in human plasma protein by a single-column high-performance liquid chromatography method with fluorescence detection. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2009;877:610–614.
24. Hanssen NM, Engelen L, Ferreira I, et al. Plasma levels of advanced glycation endproducts Nε-(carboxymethyl)lysine, Nε-(carboxyethyl)lysine, and pentosidine are not independently associated with cardiovascular disease in individuals with or without type 2 diabetes: the Hoorn and CODAM studies. *J Clin Endocrinol Metab*. 2013;98:E1369–E1373.
25. Scheijen JL, Schalkwijk CG. Quantification of glyoxal, methylglyoxal and 3-deoxyglucosone in blood and plasma by ultra performance liquid chromatography tandem mass spectrometry: evaluation of blood specimen. *Clin Chem Lab Med*. 2014;52:85–91.
26. Fokkens BT, Los LI, Hooymans JMM, Smit AJ. Skin autofluorescence and vitreous pentosidine in proliferative vitreous retinopathy. Abstract presented at the 11th International Symposium on the Maillard Reaction. Nancy, France, September 18, 2012.
27. El-Asrar AM, Missotten L, Geboes K. Expression of high-mobility groups box-1/receptor for advanced glycation end products/osteopontin/early growth response-1 pathway in proliferative vitreoretinal epiretinal membranes. *Mol Vis*. 2011;17:508–518.
28. Bu S-C, Kuijer R, Li X-R, Hooymans JM, Los LI. Idiopathic epiretinal membrane. *Retina*. 2014;34:2317–2335.
29. Adelman RA, Parnes AJ, Michalewska Z, Ducournau D; for the European Vitreo-Retinal Society (EVRS) Retinal Detachment Study Group. Clinical variables associated with failure of retinal detachment repair: the European vitreo-retinal society retinal detachment study report number 4. *Ophthalmology*. 2014;121:1715–1719.
30. Williamson TH, Lee EJK, Shunmugam M. Characteristics of rhegmatogenous retinal detachment and their relationship to success rates of surgery. *Retina*. 2014;34:1421–1427.
31. Mitry D, Awan M, Borooah S, et al. Surgical outcome and risk stratification for primary retinal detachment repair: results from the Scottish Retinal Detachment study. *Br J Ophthalmol*. 2012;96:730–734.
32. Wickham L, Bunce C, Wong D, Charteris DG. Retinal detachment repair by vitrectomy: simplified formulae to estimate the risk of failure. *Br J Ophthalmol*. 2011;95:1239–1244.
33. Heussen N, Feltgen N, Walter P, et al. Scleral buckling versus primary vitrectomy in rhegmatogenous retinal detachment study (SPR Study): predictive factors for functional outcome. Study report no. 6. *Graefe's Arch Clin Exp Ophthalmol*. 2011;249:1129–1136.
34. Marmor MF. New hypotheses on the pathogenesis and treatment of serous retinal detachment. *Graefe's Arch Clin Exp Ophthalmol*. 1988;226:548–552.
35. Liu B, Deng T, Zhang J. Risk factors for central serous chorioretinopathy: a systematic review and meta-analysis. *Retina*. 2016;36:9–19.
36. Los LI, van der Worp RJ, van Luyn MJA, Hooymans JMM. Age-related liquefaction of the human vitreous body: LM and TEM evaluation of the role of proteoglycans and collagen. *Invest Ophthalmol Vis Sci*. 2003;44:2828–2833.
37. Bishop PN, Holmes DF, Kadler KE, McLeod D, Bos KJ. Age-related changes on the surface of vitreous collagen fibrils. *Invest Ophthalmol Vis Sci*. 2004;45:1041–1046.

Investigative Ophthalmology & Visual Science

Downloaded From: http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/935913/ on 03/02/2017